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Reviewers Belatedly Question EPA's 'Likely' Cancer Listing For Dioxane

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Experts reviewing EPA's draft assessment setting first-time inhalation risks for 1,4-dioxane, a ubiquitous Superfund contaminant, are questioning the agency's already final decision to set the chemical's listing to "likely human carcinogen," raising doubts about prospects for revising the classification.

Dioxane has long been a concern in drinking water and at Superfund sites, and in recent years environmentalists and public health groups have questioned its appearance in consumer products like soaps and shampoos.

In 2007, the Agency for Toxic Substances & Disease Registry listed the chemical among the top contaminants at waste sites. Data on EPA's website says the greatest risk stems from low-level inhalation by workers exposed to the chemical.

In 2010, the agency issued a final Integrated Risk Information System (IRIS) assessment that listed the chemical as a "likely" carcinogen and set risk values for oral exposures. Industry and other federal agencies, including the Defense Department (DOD), the National Aeronautics & Space Administration (NASA) and the White House Office of Management and Budget (OMB) questioned EPA's strict estimate of cancer risks by oral exposure. The cancer slope factor was 17 times more potent than the one in EPA's 1990 IRIS assessment.

One year later, the agency issued a revised draft assessment of the chemical's inhalation risks that was based on new toxicity studies that industry opponents had recommended to question EPA's calculation of dioxane's oral cancer risks.

The draft calculates a reference concentration (RfC), or the largest amount of the chemical that EPA anticipates can be inhaled daily over a lifetime without adverse effects, of 3x10^-2 milligrams per cubic meter (mg/m^3).

EPA staff used the same study as the basis for their cancer risk number, or inhalation unit risk, of 5x10^-6 (nanograms/m^3)^-1. Both numbers represent the first time EPA has produced inhalation risk estimates for 1,4-dioxane.

The draft also reiterated its previous conclusion that the substance is a "likely" carcinogen.

But the panel reviewing the new draft assessment -- with red-lined additions of the inhalation risk discussion and calculations -- split on their comments addressing dioxane's carcinogenicity. Panelist James Bruckner, a professor at the University of Georgia's College of Pharmacy, stated that he did "not believe the overall strength of scientific

data is strong enough to classify dioxane as a 'likely human carcinogen.' The category 'possible human carcinogen' is more appropriate." Bruckner argued that there is no evidence of cancer in human studies, while genotoxicity studies are also largely negative. "Very high chronic oral or inhaled doses are required to produce tumors in rodents . . . I doubt that low, environmentally-encountered levels of dioxane pose a significant cancer risk to humans."

Another panel member, David Dorman, writes, "EPA has not justified their selection of 'likely to be carcinogenic to humans' for the inhalation route. I don't disagree with this selection; however, a more transparent application of the Guideline's 'criteria' would be beneficial." Dorman, a professor of toxicology at North Carolina State University's College of Veterinary Medicine, was also a member of the National Academy of Sciences (NAS) panel that reviewed EPA's draft IRIS assessment of formaldehyde, and found evidence lacking in the agency's conclusions regarding leukemia. Dorman is also slated to serve on the newly announced NAS panel that will review EPA's IRIS assessment program.

And a third panelist, consultant Frederick Miller, also disagrees with the classification and appears to question the agency's classification system. While the agency "adequately made" the case that the listing complies with its 2005 cancer guidelines' criteria for "likely" carcinogens, the probability of the chemical causing any cancer is "probably nonexistent" because exposures are "about 500,000-fold lower than the lowest exposure level used" in the main study EPA relies on, because "1,4-dioxane is not genotoxic in the vast majority of mammalian assays and does not affect DNA repair," Miller writes. *The reviewers' comments are available on InsideEPA.com.* (*Doc ID: 2403836*)

By contrast, other panelists agreed with EPA's cancer classification. Raghubir Sharma, a professor emeritus at the University of Georgia's College of Veterinary Medicine, called the proposed classification "appropriate."

"Given the evidence of multiple tumor sites by multiple routes of exposure and considering the lack of information on the mode of action for 1,4-dioxane carcinogenicity, I think the characterization as likely to be carcinogenic to humans is justified," writes panelist Panelist Harvey Clewell III, a senior investigator at the Hamner Institutes for Health Sciences.

Panelist Ronald Melnick's support appears more muted. Melnick, a consultant, pointed to EPA's criteria in expressing his support for the conclusion. "1,4-Dioxane induced tumors at multiple sites, in multiple species, in multiple studies, and by inhalation or drinking water exposures. Thus, the conclusion that 1,4-dioxane is 'likely to be carcinogenic to humans' by all routes of exposure is consistent with recommendations in EPA's cancer risk assessment guidelines for choosing a weight-of-evidence descriptor for human carcinogenic potential."

The panelists' split follows a similar split among comments from other federal agencies, which EPA collected last year. Comments from the DOD, NASA and OMB all questioned EPA's decision to calculate dioxane's inhalation cancer risk with conservative linear modeling. This approach assumes that no level of exposure to the chemical is safe; EPA uses it when it cannot determine how a chemical causes cancer, or its mode of action (MOA).

For example, DOD's June 15, 2011, comments state that it recommends "using a nonlinear approach for low dose extrapolation of cancer risk. At the very least, both approaches should be presented, and qualitatively and quantitatively compared. If EPA still asserts that the MOA information for liver tumor formation is insufficient to move from the default linear extrapolation methodology, it should be clearly stated as a scientific policy determination, and the quantitative impact of that decision presented."

By contrast, the National Institute of Environmental Health Sciences (NIEHS) and the Centers for Disease Control & Prevention praised the draft IRIS assessment. NIEHS, in particular, indicated EPA had performed an "outstanding job." In its June 3, 2011, comments, NIEHS recommended EPA delete two tables describing potential MOAs for 1,4-dioxane "since there is no data available for any of the mode-of-action assumptions." -- *Maria Hegstad*

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